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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,152	03/20/2002	Heinrich Leonhardt	101195-70	6299

27387 7590 03/03/2004

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,152	LEONHARDT ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *10-13* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment and Response filed 16 January 2004 has been received and entered in full. Claims 1-9 have been cancelled and claims 10-13 have been added.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. All Rejections of claims 1-5 as set forth at pp. of the previous Office Action (17 September 2003) are *moot* in view of Applicant's cancellation of said claims (16 January 2004).

Claim Objections

4. Claims **11-13** are objected to because of the following informalities: both claims depend from claim 9, a cancelled claim. Appropriate correction is required. For the purposes of examination, the Examiner has treated claims 11-13 as if they depended from claim 10 to expedite prosecution (MPEP §707).

Claim Rejections - 35 USC § 112

5. Claims **10-13** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a fusion protein selected from the group consisting of VP22-SV40 T antigen, VP22-viral cyclin K, and VP22-viral cyclin V*, does not reasonably provide enablement for *a tissue regenerating agent or other fusion proteins*. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

6. The claims are drawn very broadly to a tissue regenerating agent comprising a fusion protein of VP22 and a protein capable of inducing the proliferation of terminally differentiated cells. The language of said claims encompasses a large genus of proteins, those which effect capable of inducing the proliferation of terminally differentiated cells. The claims also read *in vitro* and *in vivo* use of the "tissue regeneration agent".

7. The specification teaches a fusion protein comprising VP22 and SV40 T-antigen with a His tag, and VP22 fused to cyclin K or cyclin V.

8. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed product as a tissue regenerating agent in a patient. The specification fails to provide any guidance for the successful use of the VP22-SV40 T-antigen fusion protein or other fusion proteins which are species of the genus of VP22 fused to a protein capable of inducing the proliferation of terminally differentiated cells. Since the resolution of the various complications in regards to targeting the role an agent in tissue regeneration is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations unspecified fusion proteins, administration protocols, dosages, and then signs and symptoms of tissue regeneration to correlate with said fusion protein.

9. In essence, it is an invitation to experiment for the skilled artisan. The skilled artisan first must determine which proteins that are capable of inducing the proliferation of terminally differentiated cells are appropriate for use. The skilled artisan must then clone (subclone) the desired protein and construct the fusion proteins. Following this, the skilled artisan must administer said test fusion proteins to animal models or patients to determine which if any have the desired effect. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

10. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide expression level *in vivo* based solely on the postulated performance of a single untested fusion protein is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed fusion proteins in *in vivo* therapeutic methods, such a disclosure would not be considered enabling since the state of tissue regeneration, especially for cardiac and nervous system tissue, is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. The following references are cited herein to illustrate the state of the art of VP22 fusion proteins.

12. On the breadth of the claims, Elliott and O'Hare (1999) "Intracellular Trafficking of VP22-GFP fusion proteins." Gene Therapy **6**: 149-151 teach that VP22 fusion proteins may be expressed at levels to low to allow the full activity of the fusion protein. In this case, the VP22-GFP protein was expressed at levels too low to detect in live cells (Figure 2). The authors note that: "*It is difficult to predict how much of a component is required to elicit a biological effect, but clearly many regulatory proteins or enzymes function at relatively low physiological concentrations.*" (pp. 151) Thus due to the breath of the claims, the skilled artisan is confronted with a level of unpredictability whether or not a given fusion protein partner of VP22 will be expressed at sufficient levels, correctly fold, or have a sufficient half-life such that it is biologically active.

13. Further regarding the breadth of the claims, the claims broadly read on use of the "tissue regenerating agent" in any milieu, including those which are notoriously unpredictable such as the central nervous system. The art teaches that the CNS is a hostile environment to regeneration and growth. The art recognizes that development is limited to embryonic and early juvenile period after which it is no longer possible in higher vertebrates such as mammals and birds. Jackowski (1995) "Neural injury repair: hope for the future as barriers to effective CNS regeneration become clearer." British Journal of Neurosurgery **9**: 303-317 teaches that two barriers prevent regeneration, growth, and repair in the central nervous system (CNS): an intrinsic inability of CNS neurons to mount a regenerative response and a CNS environment that is non-supportive or actively inhibitory to neural regeneration (pp. 305-311). Therefore the

claims as instantly presented run contrary to the teaching of the art where "regeneration", "growth", and "development" in the CNS have high hurdles to overcome. The instant Specification does not teach nor adequately address how the skilled artisan is to surmount these obstacles when using the invention.

14. On the nature of the invention, Derer *et al.* (1999) "Direct protein transfer to terminally differentiated muscle cells." J. Mol. Med. 77: 609-613 teach that a VP22-GFP fusion protein can successfully enter terminally differentiated cells, in this case myotubes (Figure 3). However, the authors note that in the unfused myotubes in the same experiment showed only nuclear localization of the VP22-GFP fusion protein versus predominately cytoplasmic localization (pp. 613). Thus a VP22 fusion protein may not accumulate in the correct subcellular compartment (cytosol versus nucleoplasm) as to be useful as a "tissue regeneration agent" for a terminally differentiated cell even though it may enter said cell. Also, as noted above, even if the protein makes it to the correct or desired subcellular location, it may not be active or present in a sufficient amount as to be biologically active. Thus the skilled artisan is confronted with an undue experimentation burden of trail and error to determine which fusion protein combinations work.

15. On working examples, Derer *et al.* (16 January 2002) "A novel approach to induce cell cycle reentry in terminally differentiated muscle cells." FASEB J. **16**(1): 132-133 teach a post-filing reduction to practice of a VP22-SV40 fusion protein which is capable of entering terminally differentiated muscle cells (Figure 1). However, this reference does not provide support for "tissue regeneration" but in fact shows that the VP22-SV40 protein, *in vitro*, can stimulate mitosis but not act as a "tissue regeneration agent". It is noted that "tissue

regeneration" can be understood to mean the revival of dead cells which is not show by said reference.

16. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from prophetic considerations of the possible effects of a single member of a large genus to the *in vivo* therapeutic use as a tissue regeneration agent as exemplified in the references herein.

17. Claim **10** is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

18. The claim requires "a protein capable of inducing the proliferation of terminally differentiated cells" while failing to require that the protein possess any particular conserved structure, or other distinguishing feature. Thus, the claims are drawn to a genus of proteins that is defined by a desired property.

19. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of desired property. The specification does not identify any particular portion of the structure that must be

conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

20. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

21. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003). In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since patent described the compound's desired function of reducing activity of enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to

discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

22. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Claim Rejections - 35 USC § 102

23. Claims **10** is rejected under 35 U.S.C. 102(e) as being anticipated by US 6,017,735 (25 January 2000) O'Hare & Elliott. US 6,017,735 teaches a fusion protein comprising VP22 fused to a protein for cell cycle control (claim 1). This includes growth factors such as GM-CSF, M-CSF, G-CSF which may be construe as "a protein for inducing the proliferation of terminally differentiated cells" thus meeting the limitations of claim 10 (Col. 12 lines 34-50). The recitation in the claims "an agent for regenerating damaged tissue" is interpreted as an intended use and is not given patentable weight in this art rejection. Also, the composition of US 6,017,735 is not inconsistent with such treatment.

24. Claims **10** and **11** are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,358,739 (19 March 2002) Baetge *et al.* US 6,358,739 teaches a fusion protein comprising VP22 fused to SV40 large T antigen or SV40 small T antigen thus meeting the limitations of claims 10 and 11 (claims 1 and 2). The recitation in the claims "an agent for regenerating damaged tissue" is interpreted as an intended use and is not given patentable weight in this art rejection. Also, the composition of US 6,358,739 is not inconsistent with such treatment.

25. Claims **10** and **11** are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,451,601 (17 September 2002) Baetge *et al.* US 6,451,601 teaches a fusion protein comprising VP22 fused to SV40 large T antigen or SV40 small T antigen thus meeting the limitations of claims 10 and 11 (claims 1 and 2). The recitation in the claims "an agent for regenerating damaged tissue" is interpreted as an intended use and is not given patentable weight in this art rejection. Also, the composition of US 6,451,601 is not inconsistent with such treatment.

Summary

26. No claims are allowed.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

28. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
February 17, 2004